INJECTABLE DUAL DELIVERY ALLOGRAPH BONE/POLYMER COMPOSITE FOR TREATMENT OF OPEN FRACTURES

PRIORITY

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 12/676,710 filed Mar. 5, 2010 which claims priority to International Application No. PCT/US2008/075481 filed on Sep. 5, 2008 which claims priority under 35 U.S.C. §119(e) of Provisional Patent Application No. 60/970,194 filed on Sep. 5, 2007 and Provisional Patent Application No. 61/294,481 filed Jan. 12, 2010. The content of these applications are incorporated herein by reference in their entirety.

GOVERNMENT SUPPORT

[0002] This invention was made with support from the US Army Institute for Surgical Research grant number DOD-W81XWH-06-1-0654 and the Orthopaedic Trauma Research Program grant number DOD-W81XWH-07-1-0211. The United States Government has rights to this invention.

BACKGROUND AND SUMMARY OF THE INVENTION

[0003] Bone regeneration is required for healing of open fractures, and healing is often complicated by chronic infection. Restoration of bone form and function is achieved through the physiological and regenerative process of bone healing. Infection is a significant clinical problem in bone fracture healing, especially for open fractures with large gaps in the bone which happens frequently in combat-related trauma, for example. Current approaches require a two-step process, in which the infection is first controlled by implantation of non-degradable tobramycin-impregnated PMMA beads, followed by implantation of a bone graft to promote bone healing. To reduce the healing time of the patient, it is desirable to promote bone fracture healing and control infection through one surgical procedure.

[0004] Biodegradable polymers have been used extensively as scaffolds to support tissue regeneration. Ideally, scaffolds should possess a three dimensional structure, high porosity with an interconnected pore structure, and a suitable surface structure for cells. Polyurethanes (PUR) have been investigated as scaffolds in bone tissue engineering due to their porous, biodegradable, and biocompatible properties. PUR scaffolds support attachment, growth, and differentiation of osteoprogenitor cells in vitro, and biodegrade to non-toxic products in vivo. Moreover, the physical and biological properties, as well as the degradation rate, of PUR scaffolds can be tuned to targeted values through the choice of intermediates used in the synthesis. Therefore, compared with currently available scaffolds and delivery systems, PUR scaffolds can offer many advantages in the design of injectable and biodegradable polymer compositions.

[0005] The recent development of injectable, biodegradable, and in situ cross-linkable biomaterials seek to alleviate many of the challenges associated with current surgical techniques and prefabricated tissue engineered implants. PUR scaffolds can be used as injectables through a two-component liquid system which cures in situ to form a solid providing a strong bond with surrounding tissues due to the following advantages. Firstly, the moderate exothermal polymerization process does not cause detrimental effects to the surrounding tissue. Secondly, the mechanical and physical properties can be tuned according to selected applications. Thirdly, the resulting polymer scaffolds allow for diffusion of nutrients, providing a cytocompatible environment and guiding cell attachment, growth, and differentiation. The scaffolds of the present invention also serve as a delivery device for drugs which promote cell infiltration and tissue remodeling. Based on the functional mechanisms of different drugs, the release profiles of them from PUR scaffolds can be controlled through adopting various including strategies. Dual release can also be achieved through embedding two different drugs in the same scaffold.

[0006] Embodiments of the present invention relate to the delivery of biologically active agents from biodegradable polyurethane scaffolds. In one embodiment, the biologically active components are incorporated as a labile powder in one of the components of the reactive polyurethane prior to mixing. Previous studies have shown that biologically active proteins with hydroxyl groups and amines, such as proteins, covalently bind to the polyurethane when dissolved in solution. For example, release of ascorbic acid from biodegradable polyurethane foams has been reported (Beckman, WO2004065450, incorporated herein by reference). However, as disclosed herein, when the protein is dissolved in solution, the cumulative release after 20 days is low (<20%). With embodiments of the present invention, substantially higher (>60%) cumulative release of the biological can be achieved. We have demonstrated release, as well as in vitro and in vivo bioactivity, for a variety of biologicals, including tobramycin (antibiotic), colistin, BSA, PDGF, and BMP-2. All of these biologicals have hydroxyl groups and amines, and yet they achieve a high cumulative release.

[0007] Bacteria in a open fracture wound, which can cause osteomyelitis and compromise fracture healing. Such contamination should be treated immediately to allow proper healing. Local delivery of antibiotics can achieve high local concentrations while systemic levels remain low. This approach is a common clinical practice and has been demonstrated in animal studies to be safe and effective for treating osteomyelitis.

[0008] While local antibiotic delivery from PMMA beads is an established clinical treatment of infected fractures, surgical removal of the beads is required before implanting a bone graft. A more ideal therapy would comprise a scaffold and antibiotic delivery system administered in one procedure. Biodegradable polyurethane scaffolds have been shown in previous studies to promote new bone formation in vivo, but their potential to control infection through release of antibiotics has not been investigated.

[0009] Additionally, local delivery of tobramycin from implanted poly(methyl methacrylate) (PMMA) cement beads is an established therapy for treating infected fractures, but only a small amount (<10%) of the drug is released. Tobramycin is a known antibiotic drug. See, for example, The Merck Index, Twelfth Edition, page 1619.

[0010] As indicated above, the PMMA beads are not resorbable and must be surgically removed after two to six weeks, at which time a bone graft is implanted to aid healing.

[0011] A much needed therapy for bone infections such as those described above would include both a delivery system and a scaffold to promote fracture healing. Preferably, the system would release the antibiotic dose over an extended period of time, biodegrade to non-cytotoxic decomposition